Title & Detailed Synopsis of the Proposed Ph.D. Thesis

Name of the Candidate: Nayana Nayek
Supervisor: Prof. Dr. Goutam Brahmachari
Chemistry Department, Visva-Bharati, Santiniketan

DESIGN AND SYNTHESES OF BIOLOGICALLY RELEVANT ORGANIC SCAFFOLDS BASED ON GREEN-INSPIRED MOLECULAR HYBRIDIZATION APPROACH

Background: Molecular Hybridization (MH), a strategy analogous to conventional combination therapy with the expectation that the two drugs are covalently linked and available as a single entity, is currently well-practiced in the process of rational drug design based on the recognition of pharmacophoric subunits in the molecular structure of two or more known bioactive derivatives which, through an adequate fusion of these sub-units, lead to the design of new hybrid architectures with extended pharmacological potential. MH is a rational drug design approach to access new chemical entities synthesized by combining two or more pharmacophoric units from different bioactive compounds (*i.e.* two or more known bioactive compounds in a single molecule), and the main objectives of this approach are: (i) improvement in properties and characteristics of the original templates without loss of biological activity; (ii) in the case of infectious and/or parasitic diseases, and cancer, compounds being less prone to drug resistance; (iii) improved pharmacological potency; (iv) increased commercial lifetime; (v) better efficacy due to simultaneous action on different biological targets (multifactorial diseases such as Alzheimer's disease, schizophrenia, inflammation, and certain CNS disorders), and (vi) synergetic, dual, or multiple drug action on different targets.

When successful synthesis brings together two pharmacophoric groups into a molecule, we obtain a hybrid composite! Better still is the hybrid species that has the ability to interact with more than one receptor and which triggers more than one biological response. We then have a multitarget hybrid chemical entity that will be a candidate for a much more interesting drug than the traditional single target drug. Most drugs are small bioactive molecules that interact with specific macromolecules or receptors, resulting in therapeutic effects. Multitarget therapy is more effective than traditional drug therapy which emphasizes maximum selectivity for a single target. By interacting with different targets, complex diseases of multifactorial origin are treated with greater effectiveness and in less time. Requiring smaller doses for simultaneous targets, multitarget therapies also feature lower toxicity, and reduced side effects.

Designing hybrid compounds as selective multi-target chemical entity is a challenge, opportunity, and new idea to better act against specific multiple targets. New hybrids compounds

often exhibit two or more activities going about as multi-target drugs (mt-drugs) and may have superior safety or efficacy. Application of integrating a range of information and sophisticated new *in silico*, bioinformatics, structural biology, pharmacogenomics methods may be useful to discover/design, and synthesis of the new hybrid molecules. Ever since planned and synthesized hybrids have been shown to exhibit multiplied activity, and act as multitarget drugs, the medicinal chemistry community quickly adopted the concept of Multi Target Drug Discovery (MTDD), or Multi Target Direct Ligands (MTDL), which have become an object of study for various research groups around the world.

This spectacular field has now created a stir among the synthetic and medicinal chemistry at large, and they have taken the dominating challenge in designing and synthesizing such hybrid molecular scaffolds to boost the ongoing development in present drug discovery programmes. At the same time, the chemical community is also aware of our environment and green chemistry aspects! Since its first proposition in the 90s, the topic of *green and sustainable chemistry* has now attained a considerable growth over the past 25 years and become much popular among the researchers working in all branches of chemical sciences. Dedicated research endeavors have yielded innumerable green products and processes so far, and such well-documented quarter century advances in the fields of *green chemistry and green engineering* have framed a solid platform that motivates and empowers the younger researchers to carry forward the *flag* with much enthusiasm and potential! Aiming on the development of processes for sustainable production of chemicals and materials, innovations in green chemistry and engineering, at molecular, process, and systems levels, are reported at an ever-increasing rate. Hence, the next 25 years of *green and sustainable chemistry* is expected to become more powerful, promising and potent finding much applications in industrial sectors.

During the recent past, various greener pathways as alternatives to traditional chemical syntheses and transformations have been invented in diverse fields of chemistry to attain sustainability through newer concepts such as step- and atom-economy and E-factor. Greener features in designing an alternative protocol for useful organic molecules and/or materials include the use of bio-renewable resources, benign reaction media (use of greener solvents or no solvent), recyclable magnetic heterogeneous catalysts or no catalyst, minimization in by-products or waste generation with efficient isolation of target product, and consideration of energy-efficiency in performing a chemical reaction by judicious screening of reaction conditions capable to carry out the transformation at ambient conditions or to make use of microwaves (MWs), ultrasound (US), visible lights and mechanical mixings (ball-milling) as *green tools* for alternative heating and activation of reactants.

At this juncture of present-day chemical scenario, my young-mind(!) has received an encouraging stimulus to undertake a dedicated research at this spectacular filed of **Molecular Hybridization (MH) coupled with Green Chemistry Consideration**.

Objectives: The present proposal aims to design and synthesis of biologically relevant organic scaffolds and their diverse functionalized libraries keeping with the views as follow:

- To develop eco-friendly one-pot multi-component methodologies to achieve high atom-economy, avoiding multi-step complex processes either at room temperature and atmospheric pressure
- To use nontoxic/less toxic and easily available chemicals as starting materials
- To use environmentally benign, cost-effective and easily available catalysts that could be recycled and reused
- To develop non-toxic or less toxic catalyst-systems
- To develop catalyst-free synthesis
- To use water and/or aqua-organo mixture (e.g. water-ethanol) as solvent
- Easy purification of the final products avoiding chromatographic separation
- To perform synthesis under focused ultrasound irradiation
- To perform synthesis using ball-milling technique

Novelty Importance of the proposed project in the context of current status: As underlined in the ***Background***, hybrid drugs containing two or more covalently linked known potential pharmacophores are, nowadays, designed to simultaneously modulate multiple targets of multifactorial diseases to overcome the side effects associated with a single drug. Ever since planned and synthesized hybrids have been shown to exhibit multiplied activity, and act as multitarget drugs, the medicinal chemistry community quickly adopted the concept of Multi Target Drug Discovery (MTDD), or Multi Target Direct Ligands (MTDL), which have become an object of study for various research groups around the world. This new field is progressing largely at a global scenario in search for novel and promising leads in the pharmaceutical and agrochemical industries, and also for others industrial purposes. The current research interest is in the search of novel molecular scaffolds as hybrids of two or more biologically promising molecular entities and their diverse functionalized derivatives, coupled with a vision to merge these developments with green chemistry aspects to the cause of sustainability of our loving earth! In addition, this is also similarly important to develop green techniques for the industry for their bulk scale production of certain molecules of interests.

Work plan: During the project tenure, the applicant plans to take up dedicated research in designing and synthesizing biologically relevant various organic scaffolds based on green-inspired molecular hybridization approach as summarized below–

- Design of targeted organic hybrids and their functionalized libraries
- Retroanalysis of the target motif and selection of cheap and commercially available substrates
- Designing for energy-efficient reaction protocols: optimization of catalyst and solvent media under suitable energy-efficient technique preferentially

- under ambient conditions
- under ball-milling
- under ultrasound irradiation

- Application of the newly developed protocols in synthesizing more complex libraries of interest

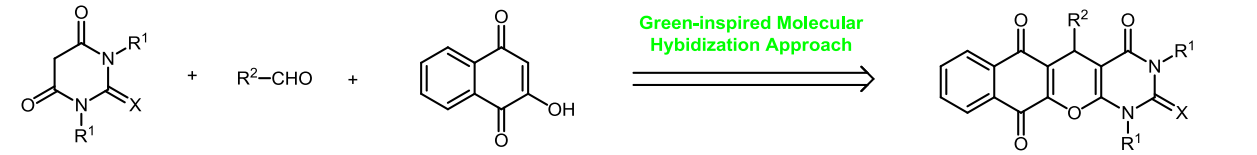
Planning to consider few more green chemistry parameters like:

- introduction of novel one-pot multicomponent technique
- to verify the reaction under catalyst-free condition
- use of efficient, non-toxic, commercially available, cheap catalyst
- use of solvent-free condition or to use suitable green solvents like water/ethanol/glycerol/PEG

Methodology: In the earlier sections, we have already mentioned in detail about the aim and the objectives of the present proposal. Simple experimental set-up is to be developed for one-pot syntheses of targeted scaffolds. The substrates and the catalyst (or catalyst-free condition) will be added in a reaction vial (at a time or in a sequential manner). If needed suitable solvent will be added into the reaction mixture. The reaction mixture will be stirred magnetically at room temperature. The progress of the reaction will be monitored by TLC/PMR. After completion, the reaction mixture will be settled down and the solvent will be removed under reduced pressure, and the residue will be purified simply by recrystallization and/or by column chromatographic technique. For characterization of the synthesized molecules, their detailed spectral studies including FT-IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, HR-MS as well as elemental analyses will be performed. In certain cases, X-ray analysis of unit crystals as to be developed of the products will also be taken care of! Similar method will be used in case of ultrasonic irradiation. Under grinding condition the reagents, substrates and catalyst (normally solid basic support) will be mixed in a ball-miller under solvent free condition. By definite programming, the reaction mixture will be subjected to grinding with pre-given speed and time. Before introduction of the reaction mixture, the particular ball-size will be chosen. After the completion, the reaction routine work up procedure will be followed to get the final products.

Some representative targeted molecular hybrids: Initially, I have screened few target hybrid organic scaffolds (**Schemes 1** to **5**) with molecular architectures containing/involving two or more pharmacophores with established potent bioactivities with an intention to generate series of diverse kind of molecular hybrids following green chemistry approach. For this purpose, I chose few pharmaceutically viable units as isatins, indoles, barbituric acids, 2-hydroxy-1,4-naphthoquinones, coumarins, uracils, 4*H*-pyrans, *etc*. with an aim to fuse among themselves to have unique molecular hybrid scaffolds based on green-inspired molecular hybridization approach.

Targeted Scheme-1:



R^1 and R^2 are diverse substituents

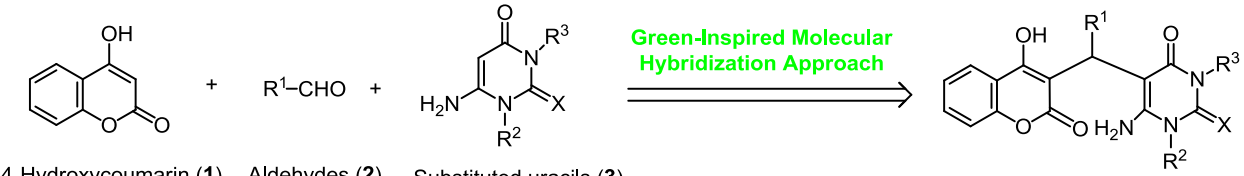
Scheme 1

Targeted Scheme-2:

R^1, R^2, R^3 are diverse substituents

Scheme 2

Targeted Scheme-3:



R^1, R^2, R^3 are diverse substituents

Scheme 3

Related Literature

[1] Koyo, O.; Takayuki, H.; Takashi, M.; Takuji, S.; Masaaki, K.; Mikihiko, N.; Yosuke, D. Development of a small hybrid molecule that mediates degradation of His-tag fused proteins. J. Med. Chem., **2017**, (DOI: 10.1021/acs.jmedchem.7b00413).

[2] Tomohiro, O.; Yoshio, A.; Mitsuo, Y.; Toshitake, K.; Shoji, F.; Yukio, T.; Tsutomu, H.; Akito, H.; Shota, I.; Manami, K.; Isaac, D. H.; Bi-Ching, S.; Hua, Z.; Tetsuji, K. Design, synthesis and evaluation of the highly selective and potent G-protein-coupled receptor kinase 2 (GRK2) inhibitor for thepotential treatment of heart failure. J. Med. Chem., **2017**, (DOI:10.1021/acs.jmedchem.7b00443).

[3] Scotti, L.; Mendonca, F. J. B.; Moura, R. O.; Ribeiro, F. F.; Ishiki, H.; Da Silva, M.; Filho, J.M..B.; Scotti, M.T. Multi-target drugs for neglected diseases. Curr. Pharm. Des., **2016**, 22(21), 3135-3163.

[4] Ribeiro, F. F.; Junior, F.; da Silva, M. S.; Scotti, M. T.; Scotti, L., Computational and investigative study of flavonoids active against trypanosoma cruzi and leishmania spp. Nat. Prod. Commun., **2015**, 10 (6), 917-920.

[5] Scotti, L.; Ishiki, H.; Mendonca, F. J. B.; Da Silva, M. S.; Scotti, M. T., In-silico analyses of natural products on leishmania enzyme targets. Mini-Rev. Med. Chem., **2015**, 15 (3), 253-269.

[6] Garuti, L.; Roberti, M.; Bottegoni, G. Multi-kinase inhibitors. Curr. Med. Chem., **2015**, 22(6), 695-712.

[7] Musso, L.; Dallavalle, S.; Zunino, F. Perspectives in the development of hybrid bifunctional antitumour agents. Biochem. Pharm., **2015**, 96(4), 297-305.

[8] Jens, K.; Jonathan, R. H.; William, D. O. H.; Thiamo, B.; Thomas, Ø. T.; Fanny, D.; Georg, J.; Anae¨lle, H.; Jutta, H. Yeast synthetic biology platform generates novel chemical structures as scaffolds for drug discovery. ACS Synth. Biol., **2014**, 3, 314−323

[9] Teiten, M.H.; Dicato, M.; Diederich, M. Hybrid curcumin compounds: A new strategy for cancer treatment. Molecules, **2014**, 19, 20839-20863.

[10] Carmen, W.; Shafinaz, C.; Georg, H.; Petia, D.; Enrico, O. P.; Peter, B.; Björn, W.; Gert, F.; Klaus, T. W.; Ralf, S. Shuttle-cargo fusion molecules of transport peptides and the hD2/3 receptor antagonist fallypride : A feasible approach to preserve ligand-receptor binding? J. Med. Chem., **2014**, 57, 4368−4381.

Nayana Nayek
(Signature of the Candidate)

Prof. Goutam Brahmachari

(Counter-Signature of the Supervisor)

Prof. (Dr.) Goutam Brahmachari
Professor of Chemistry, Chemistry Department
VISVA-BHARATI (a Central University)
SANTINIKETAN-731235, West Bengal, India
E-mail: brahmg2001@gmail.com
goutam.brahmachari@visva-bharati.ac.in
Cell: 91-9434385744